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REVIEW ARTICLE

Environmental exposure and health effects in a highly polluted area of Northern Italy: a narrative review

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Abstract

Human health and well-being are strongly linked to the state of the environment. The high industrial pressure present in the Province of Brescia, located in Northern Italy, produced strong environmental and health concerns. This narrative review of the literature aims at identifying the studies focused on the association between exposure to environmental pollutants and health effects in the population living in this area. Thirteen papers fitted the inclusion criteria: five were focused on the connection among pollutants present in air matrix and health effects, seven on both air and soil, and one on soil. No study investigated the relationship with water pollution. The great variability in the analyzed end-points made it difficult to draw precise conclusions, but the fact that, in almost all the studies, the investigated health effects have a positive association with the exposure to different kinds of pollutants, allows us to hypothesize that the considered population is living in an area where the "environmental pressure" could produce significant health effects in the future.

Keywords Environmental pollution · Environmental exposure · Environmental pressure · Health effects · High-polluted area · Public health

Introduction

Human health and well-being are strongly linked to the state of the environment. Good quality environments can provide multiple benefits to physical, mental, and social well-being (WHO 2013; EEA 2015). By contrast, environmental pollution can have negative effects on health, especially on vulnerable categories of people, such as children and the elderly (Simoni et al. 2015; Cao et al. 2016; Flores-Pajot et al. 2016; Veras et al. 2017; García-Esquinas and Rodríguez-Artalejo 2017). Air pollution (as outdoor particulate matter) is a leading contributor to mortality, with 289,000 deaths only in high-income European regions (IARC 2015; WHO 2016), as well as water and soil pollution, that strongly could affect human health (Villanueva et al. 2014; Swartjes 2015).

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The Po Valley, located in Northern Italy, is one of the most anthropized and polluted areas in Europe (Ricciardelli et al. 2017; Carnevale et al. 2015), where systematic exceeding of limit values of PM and ozone occurs (Regione Lombardia 2012; EEA 2016). High industrial pressure along the territory (Istituto Nazionale di Statistica 2015; Provincia di Brescia, Geoportale 2018) and geographical conformation caused environmental concern in this region.

Brescia and its surrounding province (one of the largest in Italy with a territory of 4800 km^2) represent an important economic center of the Po valley, with a great economic development started in the early twentieth century, with a variety of industries and sectors (steel industries, mechanical activities, and chemical implants) (Corsini and Zane 2014). In this area live over 1.2 million inhabitants with a demographic density (expressed as number of inhabitants per km^2) of 2177 and 264, respectively, for the municipality of Brescia and its province (UrbiStat 2018 http://ugeo.urbistat.com/AdminStat/en/it/classifiche/densita-demografica/comuni/brescia/17/3).

The Province of Brescia currently is an area with a very high concentration of industrial companies (almost 120,000 manufacturing companies with more than 162,000 workers) (Camera di Commercio di Brescia 2017).

As discussed by Corvalán et al., beyond the huge benefits, the modern industrial development could generate many hazards for the environment and human health (Corvalán et al. 1999). Indeed, in the Province of Brescia, all the environmental matrices were (or still are) polluted by different industrial activities. Tap water was polluted by heavy metals (Sorlini et al. 2014a), in particular hexavalent chromium (Osservatorio Acqua Bene Comune 2015) and arsenic (Sorlini et al. 2014b). Metals were also present in home gardens soil, with a contamination of some kind of vegetables (Borgese et al. 2013; Ferri et al. 2015). High amounts of organic and inorganic mutagens/carcinogens were detected in fine air particulate (Monarca et al. 1997; Turrio-Baldassarri et al. 2008; Hou et al. 2011; Ceretti et al. 2015). The quality of lake waters was impaired by the presence of cyanobacteria that produced harmful cyanotoxins (Sorlini et al. 2013). Moreover, from 2003, Brescia is included in the National Land Reclamation list (Ministero dell'Ambiente e della Tutela del Territorio 2003) due to the consistent concentration of PCBs, classified as persistent organic pollutants. In the city, there is the Site of National Interest (SIN) Caffaro, a organochlorine compound-producing factory that is the major one responsible for the presence of high concentrations of PCBs in soil, surface water, vegetables, chicken eggs, and cow milk (Turrio-Baldassarri et al. 2009) (Fig. 1).

The aim of this narrative review is to analyze the extant literature to identify the studies that measured and associated the exposure to environmental pollutants to the presence of health effects in the population living in Brescia and its province.

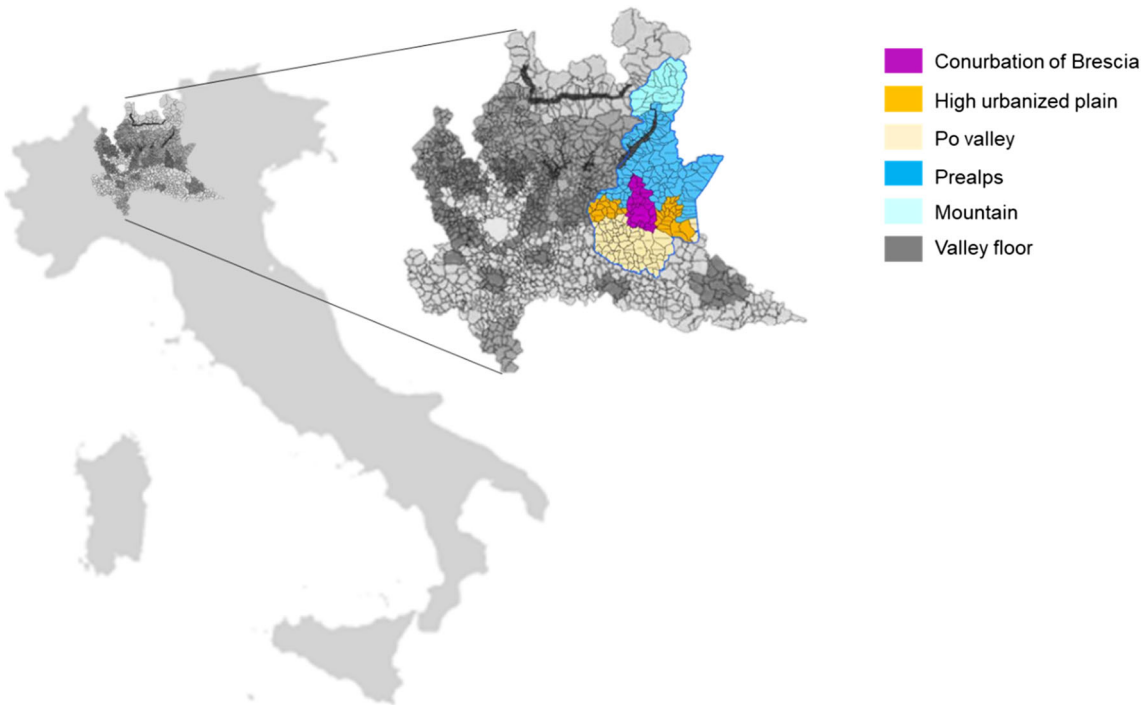

Fig. 1 Geographical position and configuration of Brescia and its Province (modified from Regione Lombardia 2012)

Methods

The review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Moher et al. 2010).

Information sources

The literature search covered the period up to October 2018. The search was performed using the PubMed database (PubMed, https://www.ncbi.nlm.nih.gov/pubmed/) and the Google search engine tool (Google Scholar).

Search strategies

The search was conducted in English and Italian using the Medical Subject Headings (MeSH) thesaurus when possible. The detailed searching strategy is summarized in Table 1.

The reference list was scanned for relevant articles up to the second level, and "related articles" of relevant ones were considered in the PubMed database or in Google Scholar. We considered the first 200 items returned by Google Scholar search.

Study selection and eligibility criteria

All the articles relevant to the search topics written in English or in Italian, with abstract and full text available, were included. Search results were merged and duplicates removed. Citations were assessed by two reviewers (CA and LB) independently and disagreement was solved by discussion and consensus or by a third reviewer (UG). We considered the following eligibility criteria: report of original data, explicit measurement of the considered environmental pollutant (the exposure must be described using specific analytic values and not with generic statements), and description of unambiguous human health impact (in terms of biomarkers of DNA damage, physiopathological parameters, pathologies, number of patients hospitalized, mortality). The methodological quality of each study was assessed independently by two authors (CA and LB) using the Kmet tool (Kmet et al. 2004). A score between 0 and 1 was assigned to each paper. Eventual disagreement was solved by consensus or by a third reviewer (UG).

Results

General findings

According to the PRISMA statement reported in Fig. 2, the search strategy returned 13 papers matching the inclusion criteria.

All the required information to perform the review were extracted and summarized in Table 2.

In 5 out of 12 papers, the authors focused their attention on air matrix (Baccarelli et al. 2009; Bertoldi et al. 2012; Ceretti et al. 2014; Rosa et al. 2016; Vaduganathan et al. 2016); in 7 out of 12, instead, the environmental pollution was studied in

Table 1 Search queries used in the systematic review

Language	Database	Search terms		
English	Pubmed	Air pollution (MeSH) Water pollution (MeSH)	AND	Brescia
		Soil pollution[a]		
		Environmental pollution (MeSH)		
		Environment (MeSH)		
		Water contamination		
		Soil contamination		
	Google Scholar	Air pollution Water pollution	AND	Brescia
		Soil pollution		
		Environmental pollution		
		Environment		
		Water contamination		
		Soil contamination		
Italian	Google Scholar	Inquinamento aria Inquinamento acqua	AND	Brescia
		Inquinamento suolo		

[a] The terms "soil pollution" did not return any result, the MeSH thesaurus readdressed to "environmental pollution"

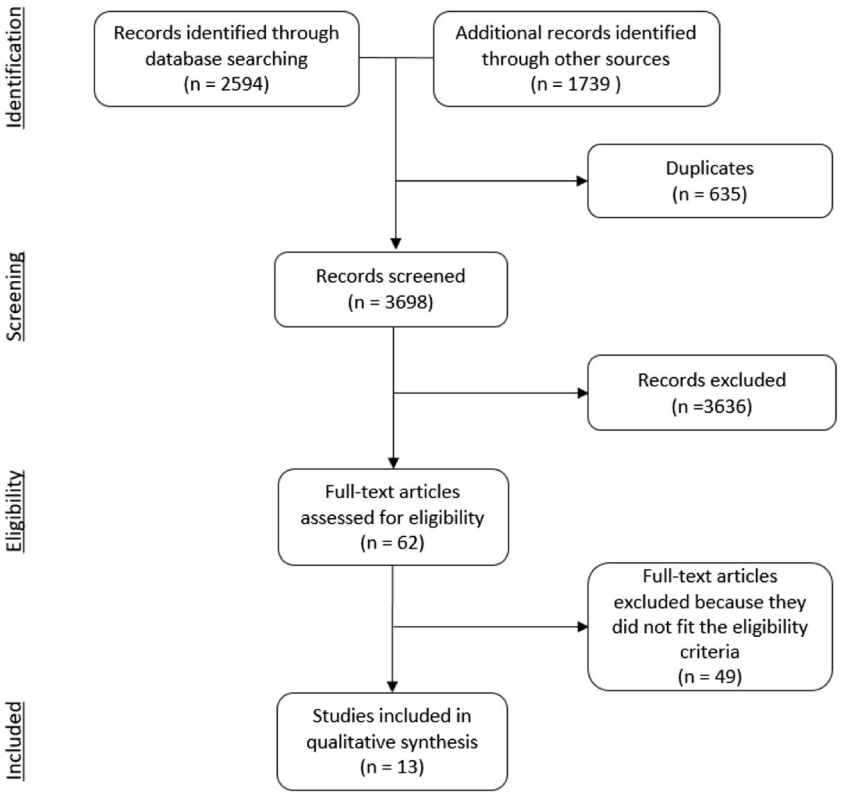

Fig. 2 Flow diagram describing the study selection according to PRISMA methodology (Moher et al. 2010)

both air and soil matrices (Donato et al. 2008; Iannili et al. 2016; Lucchini et al. 2012a, b, 2007; Squitti et al. 2009); only one paper considered the pollution present in soil (Maifredi et al. 2011). None of the selected papers reported studies on the water matrix. The assigned quality scores ranged from 0.7 to 0.9 (mean Kmet score 0.88 ± 0.08).

The length of observation time presented in the selected articles is variable (Fig. 3) ranging from 6 months (Ceretti et al. 2014) to 168 months (Maifredi et al. 2011).

The number of subjects living in the Province of Brescia included in the selected papers is also variable (Fig. 4), ranging from 14 subjects (Iannili et al. 2016) to 6000 (Vaduganathan et al. 2016).

Table 3 summarizes the age grouping of population in the selected studies. The frequency of micronuclei was studied in young children (3–6 years old) (Ceretti et al. 2014), while risk of asthma (Rosa et al. 2016) and neurobehavioral and cognitive functions (Lucchini et al. 2012a, b; Iannili et al. 2016) were investigated in adolescents (11–14 years old). Parkinsonian disorders (Lucchini et al. 2007), thyroid hormones modifications (Donato et al. 2008), and presence of cutaneous malignant melanoma (Magoni et al. 2018) were evaluated in adults and the elderly (more than 18 years old). Non-Hodgkin lymphoma cases (Maifredi et al. 2011) were investigated in the elderly from 65 to 75 years old. All age categories were correlated with cardiovascular and respiratory diseases (Bertoldi et al. 2012).

Association between environmental pollution and acute/chronic health effects

Health impacts could be also divided in two categories: acute and chronic impacts. Figure 5 describe the selected studies according to this. Few papers used as end-point the acute impact of hospitalization in the analysis of the association between PM10 and NOX and CVD and RD (Bertoldi et al. 2012; Vaduganathan et al. 2016) and in the association between PCBs and CMM (Magoni et al. 2018). Instead, the majority of authors chose various parameters of chronic impact, such as biomarkers of damage (Ceretti et al. 2014) and physiological alterations to analyze the impact of air pollution (Baccarelli et al. 2009), heavy metals (Lucchini et al. 2007, 2012a, b; Squitti et al. 2009; Iannili et al. 2016; Rosa et al. 2016), or PCBs (Donato et al. 2008; Maifredi et al. 2011).

Three papers considered the association between the hospitalization and pollutants present in the Brescia area: two papers described acute health impacts of PM10 and NO_X in terms of hospitalizations due to acute CV and respiratory diseases. CV diseases are associated with the increase of PM10 concentration, even below the current limit set by the European Union (50 μg/m^3 averaged over a 24-h period) (Vaduganathan et al. 2016). Another evaluation of air pollution and health effects was done by Bertoldi and co-workers, with a case-control study on acute effects of air emission of a cement plant on children and adults. They found an association between NO_X

Table 2 Studies with a link between environmental pollution and health impacts on people living in the Province of Brescia

Env. matrix	Author, year	Area	Characteristics of the area	Typology of the study	Type of pollutant-period of exposure	Observation time	Number of subjects	Age of subjects in years	Health impact/ biological damage marker	Main results	Kmet score
Air	Baccarelli et al. 2009§	BG/BS geographical area (Lombardy divided in five areas)	Urban and suburban area with population > 15,000 inhabitants living near major traffic roads	Case-control study	Air pollution (PM10 averaged over the 365 days preceding the index date)	From January 1995 to September 2005	663 cases, 859 controls	18–84	Deep vein thrombosis	BG/BS: OR 0.32 $p = 0.20$; Total: the risk of DVT increased in association with proximity to major traffic roads	0.9[a]
Air	Bertoldi et al. 2012	Rezzato and Mazzano	Highly industrialized and densely populated area in the surroundings of a cement plant	Cross-sectional	Cement plant emissions (NOx). Pollutant emissions monitored during two 20-day campaigns: September 2006 and January 2007	From January 2002 to December 2005	2209 adults and 277 children	Children 0–14; adults > 34 (people from 15 to 34 years were excluded from the analysis because of the small number of hospital admissions)	Cardiovascular and respiratory disease	OR 1.67 (95% CI 1.08–2.58) for the moderately exposed category (E1), OR 1.88 (95% CI 1.19–2.97) for the highly exposed category (E2), with an attributable risk of 38% of hospital admissions due to the exposure to cement plant exhausts. Adults had a weaker risk: OR 1.38 (95% CI 1.18–1.61) for group E1, OR 1.31 (95% CI 1.10–1.56) for group E2; the attributable risk was 23%	0.8
Air	Ceretti et al. 2014	Brescia	Urban with great traffic load	Cross-sectional	Air pollution: CO, NO_2, SO_2, benzene, O_3, PM10, and PM2.5—daily concentration in winter 2012 and winter 2013	Winter 2012 and winter 2013	181	3–6 (4.3 ± 0.9)	Micronuclei frequency (mean 0.29 ± 0.13)	Coefficient of linear regression for PM10 = 0.01[a] and NO2 = 0.03[a] 1 week preceding biological sample and PM2.5 = −0.03[a] 3 weeks preceding biological sample	0.7
Air	Rosa et al. 2016	Bagnolo Mella, Valcamonica, and Garda Lake	Suburban areas with varying Mn levels due to different ferroalloy activities	Cross-sectional	Air pollution (heavy metals and PM10 as co-pollutant—24 h concentration with personal sampling)	Not declared	280	11–14	Parental report of asthma; asthma medication use; wheeze; nasal allergy/hay fever	Associations between concentrations of Mn (RR 1.09, 95% CI [1.00, 1.18] per 42 ng/m^3 increase), Ni (RR 1.11, 95% CI [1.03, 1.21] per 4 ng/m^3 increase), and Cr (RR 1.08, 95% CI [1.06, 1.11] per 9 ng/m^3 increase) and parental report of asthma. Significant associations between increased Mn and Ni and increased risk of asthma medication use in the past 12 months (RR 1.13, 95% CI [1.04, 1.29] and (RR 1.13, 95% CI [1.01, 1.27], respectively)	0.9
Air	Vaduganathan et al. 2016	Brescia	Urban and suburban areas with high degree of industrialization	Cross-sectional	Air pollution (PM10—daily concentration) from September 2004 to September 2007	From September 2004 to September 2007	6000	Not declared	Acute cardiovascular events (23% with a primary diagnosis of	Increase of 1 μg/m^3 PM10 at lag 0-day: RR 1.004, 95% CI 1.002 to 1.006. Similar results for CV hospitalization risk were	0.8

Table 2 (continued)

Env. matrix	Author, year	Area	Characteristics of the area	Typology of the study	Type of pollutant-period of exposure	Observation time	Number of subjects	Age of subjects in years	Health impact/ biological damage marker	Main results	Kmet score
									AHF, 54% with ACS, 9% with MVA, and 14% with AF)	obtained using PM10 lag 3-day data	
Air/soil	Donato et al. 2008	Brescia divided in four areas	High population exposure to PCBs	Cross-sectional population--based	Total PCBs and PCB 153 contamination (serum level)	Not declared	527	20–79 (6 age groups)	Thyroid hormone levels (serum TT3, TT4, FT3, FT4, TSH, anti-TPO, and anti-TGA concentrations)	Weak inverse correlation (Spearman's coefficient below 0.2) of lipid-adjusted total PCB with FT3 and TSH, and of congener 153 with FT3 and TSH serum levels and no correlation of PCBs with FT4, TT4, and TT3 levels. However, multiple regression analysis showed weak associations of total PCB ($p = 0.05$) with FT3 and of PCB153 with free T3 ($p = 0.04$) and no association with TSH, adjusting for age, gender, and BMI	0.9
Air/soil	Iannili et al., 2016	Bagnolo Mella, Valcamonica and Garda Lake	Suburban areas with different levels of Mn (or industrial) contamination	Control-exposed pilot study	Environmental exposure to Mn (airborne and soil Mn concentration)	Not declared	10 cases and 4 controls	Cases group 14.7 ± 2.4 and control group 14.6 ± 0.5	Olfactory function	Environmental exposure to Mn from childhood to pre-adolescence can jeopardize olfactory functions: reduce subjective odor sensitivity and reduce the volume of olfactory eloquent brain structures	0.8
Air/soil	Lucchini et al. 2007	Province of Brescia	Highly industrialized area (four ferroalloy industries)	Prevalence study	Airborne Mn concentration	Environmental monitoring: inside the plants 1987/1995/1978/2-007; airborne outside the plants: 2001 Cases identification: from January 2001 to December 2001	2677 cases of Parkinso-nian disorders	18–100 (75.7 ± 10.8)	Parkinsonian disorders	Significantly higher SMRs (Kruskal–Wallis $\chi 2$ (1 df) = 17.55, $P < 0.001$) were observed in 37 municipalities in the vicinities of ferromanganese industries (standardized prevalence 492/100,000; 95% CI 442.80–541.20), compared to the other 169 municipalities of the province (standardized prevalence 321/100,000; 95% CI 308.80–333.20).	0.8
Air/soil	Lucchini et al. 2012a	Valcamonica and Garda Lake	Suburban area with ferromanganese industries; Garda Lake as reference area	Cross-sectional	Airborne and soil Mn concentration (in addition to blood, urine, and hair). Metals measured in airborne particulate matter with a 24-h	Not declared	311	11–14	Neurobehavioral functions	Subclinical deficits in olfactory and motor function. Significant impairment of motor coordination ($p = 0.0005$), hand dexterity ($p = 0.0115$), and odor identification ($p = 0.003$) associated with soil Mn.	0.9

Table 2 (continued)

Env. matrix	Author, year	Area	Characteristics of the area	Typology of the study	Type of pollutant-period of exposure	Observation time	Number of subjects	Age of subjects in years	Health impact/ biological damage marker	Main results	Kmet score
					personal air monitoring					Tremor intensity was positively associated with blood ($p = 0.005$) and hair ($p = 0.01$) Mn	
Air/soil	Lucchini et al. 2012b	Valcamonica and Garda Lake	Suburban area with ferromanganese industries; Garda Lake as reference area	Cross-sectional	Airborne and soil Mn concentration (in addition to blood, urine, and hair)	Not declared	299	11–14	Cognitive function and behavior	Significant negative association between BPb level on IQ and a borderline positive correlation between BPb and hyperactivity in adolescents.	0.9
Air/soil	Magoni et al. 2018	Brescia town, Brescia province excluding town and outside province	Urban and suburban areas with high degree of industrialization	Case-control	Total PCBs and 33 PCB congeners contamination (serum level)	Hospital admissions: from July 2014 to November 2016	205 cases and 205 controls	Cases 55.1 ± 14.2 Controls 54.9 ± 14	CMM diagnosis	No significant association were found between CMM and log-transformed total PCB serum levels whereas strong positive association was found between CMM and phenotypic, constitutional characteristics, and UV exposure. Distribution of total PCBs serum levels did not approximate the normal distribution. Several PCB congeners were not detected in all or almost all subject whereas congeners 138,153,and 180 were found in the majority of subjects. Association with wide confidence interval was observed for previous occupation in the agricultural (OR = 1.69) or chemical sector (OR = 2.23).	0.9
Air/soil	Squitti et al. 2009	Valcamonica and Brescia	Urban and suburban areas with strong presence of ferromanganese industries; Brescia as reference area	Case-control	Airborne and soil Mn concentration	From January 2001 to December 2001	93 parkinsonian cases and 76 controls	Valcamonica cases 71.66 ± 8.5, Brescia cases 66.86 ± 9.5; Valcamonica controls 67.90 ± 7.1, Brescia controls 68.29 ± 11.1	Serum Cu, Zn, Fe, and Mn in blood (MnB) and urine (MnU), transferrin, peroxides, alanine and aspartate transaminases, and direct bilirubin	Valcamonica patients had higher serum levels of Cu and AST/ALT ratio, but lower Zn and Fe concentrations in comparison with the other subgroups of cases and controls. Within the parkinsonian group, the semi-parametric multiple regression model showed that both Cu and AST/ALT ratio positively associated with UPDRS III score	0.9
Soil	Maifredi et al. 2011	Brescia divided in four areas	Areas close to a PCB-producing	Case-control		New diagnosis of NHL: 1993–1995	495 NHL cases and	Cases 68.3 ± 14.2 Controls 68.2 ± 14.3	Non-Hodgkin's lymphoma	An association was found for having resided 10–19 years	0.9

Table 2 (continued)

Env. matrix	Author, year	Area	Characteristics of the area	Typology of the study	Type of pollutant-period of exposure	Observation time	Number of subjects	Age of subjects in years	Health impact/ biological damage marker	Main results	Kmet score
			factory (from A to C) with different PCB soil concentrations		PCB contamination. Three definitions of time exposure	and 1999–2001; deceased cases: 1990–2004	1467 controls			in area A (OR = 3.8; $p = 0.005$) and in the polluted areas considered together (A + B + C) (OR = 1.7; $p = 0.04$). A linear trend next to the cut-off of statistical significance was present for the polluted areas considered together (A + B + C) ($p = 0.06$). When we restricted the analysis to incident cases, we found a statistically significant association for having resided 10–19 years in area A (OR = 4.0; 95% CI 1.4–11.7; $p = 0.01$), but not for the polluted areas considered together	

§The paper did not describe explicitly data on the province of Brescia, but presented elaboration of regional datasets in which Brescia was assimilated to homogeneous areas

[a] The Kmet score was assigned on the basis of the entire study

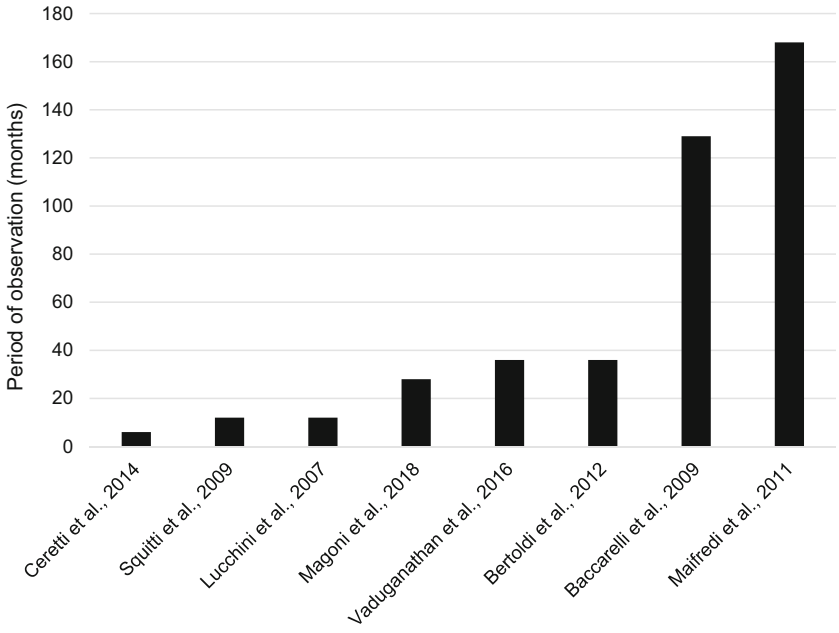

Fig. 3 Length of the period of observation in the selected studies. Five studies were not included in the graph because periods of observation were not clearly declared

concentrations and the risk of hospitalization for cardiovascular or respiratory disease, especially in children. In particular, it was estimated that 38% of children hospitalization could be avoided if the NOx concentration was below 110 μg/m^3, in the considered areas (Bertoldi et al. 2012). Magoni et al., instead, examined the acute health impacts in terms of hospitalization due to CMM diagnosis and its association with PCB serum levels and specific PCB congeners, considering also the main risk factors for the melanoma. They found association between CMM and some phenotypic, constitutional characteristics and UV exposure but that the hypothesis of the investigated association was not supported by the case-control study and no relation was found between risk of CMM and total PCB plasma levels. Considering the 33 PCB congeners, they found that most of them were not observed in cases ($n = 205$) and in controls ($n = 205$).

Eight papers described chronic traits of impacts of pollution through the analysis of biomarkers of early effect or pathologies. Only one group used the frequency of MN as a biomarker of air pollution exposure. They analyzed the DNA damage in exfoliated buccal mucosa cells of healthy 3–6-year-old children living in the urban area of Brescia.

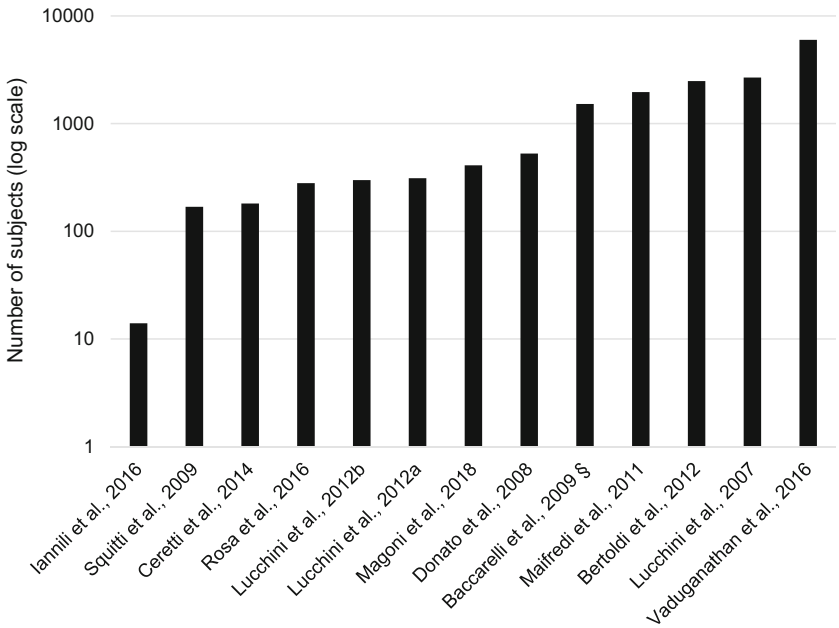

Fig. 4 Number of subjects included in the selected studies. § = the paper did not describe explicitly data on the Province of Brescia, but presented elaboration of regional datasets in which Brescia was assimilated to homogeneous areas

Table 3 Age grouping of health parameters measured in individuals exposed to various environmental pollutants

Age groups (years)			Pollutants: PM10 and PM2.5	CO, NO_2, SO_2, benzene, O_3	Metals (Fe, Zn, Cu, Mn, Pb)	PCBs
	Young	**0–3**		CVD and RD (Bertoldi et al. 2012)		
		3–6	MN (Ceretti et al. 2014)	MN (Ceretti et al. 2014)		
		11–14	Asth (Rosa et al. 2016)		Asth (Rosa et al. 2016); NBF (Lucchini et al. 2012a); CFB (Lucchini et al. 2012b); OF (Iannili et al. 2016)	
		15–17				
	Adults	**18–30**	DVT (Baccarelli et al. 2009)		PD (Lucchini et al. 2007); Thy (Donato et al. 2008)	CMM (Magoni et al. 2018)
		31–34				
		35–50		CVD and RD (Bertoldi et al. 2012)		
		51–65				
	Elderly	**65–75**				NHL (Maifredi et al. 2011)
		75–84				
		>84				

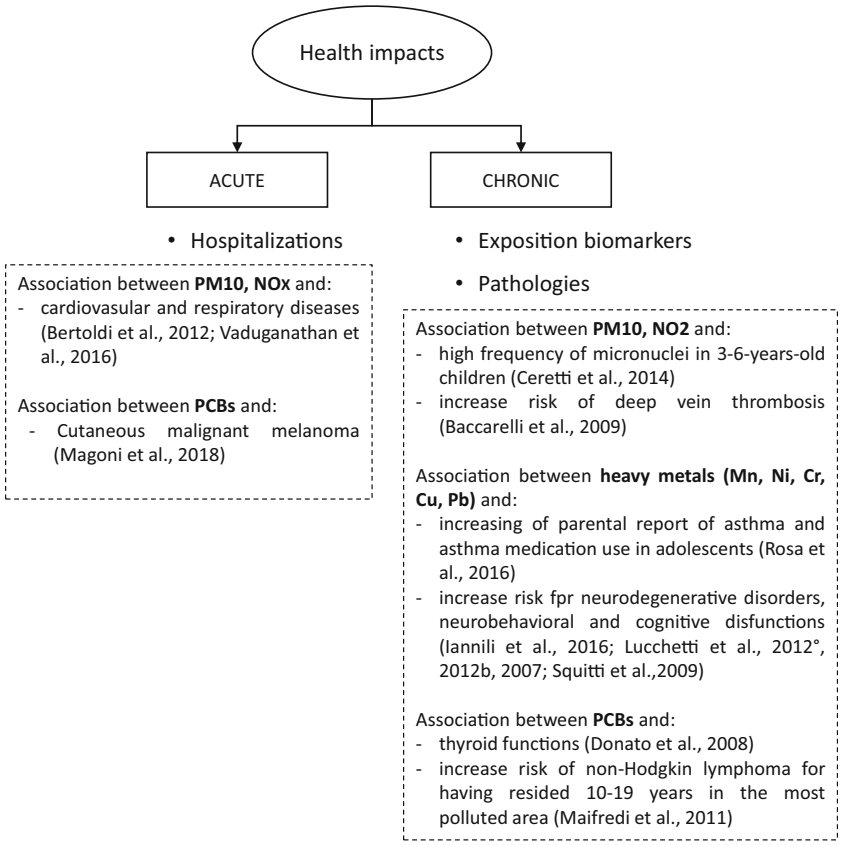

Fig. 5 Health impacts of different environmental pollutants reported in the included studies

Children exposed to high levels of air pollutants (PM10, PM2.5, and NO_2) in winter have a high frequency of MN in buccal mucosa cells (mean ± SD = 0.29 ± 0.13), higher than usually found in children living in areas with medium/high levels of air pollution (Ceretti et al. 2014). The air pollution, measured as concentration of PM10, was also associated with an increased risk of deep vein thrombosis development, correlated with the distance from major traffic roads (OR = 1.74, living 3 m from a major road). Despite the overall result, the risk for the population of Brescia had an OR = 0.32, probably due to the restricted number of subjects involved (Baccarelli et al. 2009). Another category of pollutants in the Province of Brescia is represented by heavy metals, especially Mn, Pb, Ni, and Cr, present in air and soil. Mn is a well-known neurotoxic agent and the prolonged environmental exposure is considered a supposed accelerator of the onset of IPD. Lucchini et al. established an association between environmental exposure to Mn and prevalence of Parkinsonian disorders in population resident in municipalities near ferromanganese plants (with a standardized prevalence of 492/100000) (Lucchini et al. 2007). Lifetime exposure to neurotoxicant metals (in particular Mn) was also correlated to an increased risk of neurodegenerative disorders when accompanied by alteration of metal metabolism due to a subclinical dysfunction of the liver (Squitti et al. 2009). Specific attention was given by many authors to the adolescents' exposure to metals, a particularly susceptible population subgroup. Parental report of asthma in 11–14-year-old adolescents was associated with Mn (RR = 1.09), Ni (RR = 1.11), and Cr (RR = 1.08) levels in sampled air. Significant associations were also found between increased risk of asthma medication use and concentrations of Mn (RR = 1.13) and Ni (RR = 1.13) (Rosa et al. 2016). A positive association between Mn in air and soil with motor coordination, hand dexterity, and odor identification and between Mn found in blood and hair with tremor was established in adolescents residing in areas with previous heavy metal emissions from ferroalloy plants (Lucchini et al. 2012a). Furthermore, a negative association between blood Pb levels and IQ was demonstrated in the same cohort of adolescents (Lucchini et al. 2012b). More recently, a pilot fMRI experiment suggested a reduction of bold signal, odor sensitivity, and olfactory bulb volume in subjects exposed to Mn (Iannili et al. 2016).

Two reports investigated the relation between serum levels of PCBs and some health aspects. Donato et al. established that the environmental exposure to relatively high PCBs levels did not alter thyroid functions, measured as hormone serum levels (Donato et al. 2008). On the other hand, some evidence for an association between

Table 4 Indicators of health damage in relation with different environmental pollutants

			Pollutants				
Categories	Indicators	Ref.	PM10	PM 2.5	CO, NO_2, SO_2, benzene, O_3	Metals (Fe, Zn, Cu, Mn, Pb)	PCBs
Biological damage	Micronuclei	Ceretti et al. 2014	▲	▲	▲		
Biochemical parameters	AST/ALT ratio	Squitti et al. 2009				▲	
	Thyroid hormones levels	Donato et al. 2008					↔
Neurobehavioral alterations	Cognitive function and behaviour	Lucchini et al. 2012b				▼	
	Neurobehavioral functions	Lucchini et al. 2012a				▼ Mn	
	Olfactory functions	Iannili et al. 2016				▼ Mn	
Pathologies	Acute cardiovascular events	Vaduganathan et al. 2016	▲				
	Asthma	Rosa et al. 2016	▲			▲	
	Cardiovascular disease	Bertoldi et al. 2012			▲ NO_X		
	Cutaneous malignant melanoma	Magoni et al. 2018					↔
	Deep vein thrombosis	Baccarelli et al. 2009	▲				
	Non-Hodgkin's lymphoma	Maifredi et al. 2011					▲[a]
	Parkinsonian disorders	Lucchini et al. 2007				▲ Mn	
	Respiratory disease	Bertoldi et al. 2012			▲ NO_X		

In grey shading are highlighted the statistically significant associations. Where explicated, it has been reported only the contaminant for which a correlation was observed

▲ increase of indicators, ▼ decrease of indicators, ↔ no variations of parameters

[a] Increase of risk found for people resident (10 years or over) in the most polluted area analyzed

PCBs exposure and an increased risk of non-Hodgkin's lymphoma was recognized (Maifredi et al. 2011).

Association between environmental pollution and different indicators of health damage

After having analyzed the selected studies from the point of view of the indicators of health damage used (Table 4), we can recognize different classes of indicators. As biological damage indicators, micronuclei were analyzed in relation to air pollutants, such as PM2.5, PM10, CO, NO_2, or SO_2 (Ceretti et al. 2014). Different biochemical parameters were analyzed: AST/ALT ratio was correlated to heavy metal concentration (Squitti et al. 2009); some thyroid hormones were analyzed to monitor the PCBs exposure (Donato et al. 2008). Several neurobehavioral alterations, such as cognitive function and behavior (Lucchini et al. 2012b), olfactory functions (Iannili et al. 2016), and neurobehavioral functions (Lucchini et al. 2012a), were analyzed to investigate the consequence of the exposure to heavy metals. Many authors focused the attention on pathologies correlated to different pollutants. Acute cardiovascular events (Vaduganathan et al. 2016) and deep vein thrombosis (Baccarelli et al. 2009) were associated to PM10 concentration. Asthma was correlated to both PM10 and heavy metals (Rosa et al. 2016). Cardiovascular and respiratory diseases (Bertoldi et al. 2012) were studied in association with the air concentration of NO_X. The onset of non-Hodgkin's lymphoma was analyzed in people exposed to PCBs (Maifredi et al. 2011) and the arising of parkinsonian disorders were evaluated in a population exposed to heavy metals (Lucchini et al. 2007).

Considered together, despite the wide range of analyzed parameters, almost all of the studies (11/13) highlighted a positive association between the pollutants and the health indicators.

Discussion

We conducted a comprehensive narrative review of published studies that evaluated the association between environmental pollution and health effects in the Province of Brescia. This is the most extended province of the Lombardy Region and represents an important industrial center. Regarding the link between industrial development and the environment in the territory of Brescia, it is noticeable that all the environmental matrices are subjected to the pollution caused by human activities. Brescia is indeed one of the affected zones with exceedance of the annual limit of PM10 for which, in April 2017, the EU Commission urges Italy to take actions against

air pollution to safeguard public health (European Commission 2017). In the urban area of Brescia, one of the 39 contaminated SIN is also located, because of the presence of high concentrations of PCBs (Ministero dell'Ambiente e della Tutela del Territorio 2003). The water quality was also impaired by Cr(VI) pollution, solved in 2015 with an abatement system based on the addition of iron sulphate (Osservatorio Acqua Bene Comune 2015; A2A 2017).

The literature concerning the surveillance of pollutants in environmental matrices in the Province of Brescia is certainly extensive, but few works relate the levels of pollutants to a measurable health effect. To the best of our knowledge, this is the first review taking into account this kind of topic. Moreover, the total absence of studies on the water system is an unexpected result, due to the abovementioned water quality impairment caused by the high concentration of Cr(VI) or other metals (Sorlini et al. 2014a) and mixture known to be genotoxic (Ceretti et al. 2016).

The mean quality Kmet score is 0.88, describing an overall high quality of the reported information but the great variability in the studies' size and especially in the analyzed end-points, made it difficult to draw precise conclusions. Nevertheless, the fact that in almost all the studies (11 out 13), the investigated health effects show to have a positive association with the pollution, allows to hypothesize that the considered population live under a recognizable environmental pressure. The two articles that did not reveal connection between pollutants and health effects investigated both the PCB serum level and specific PCB congeners.

Our narrative review presents some limitations: our findings were limited by the quantity, the heterogeneity of reported data, and the diversified end-points. Moreover, the case study area is not extensively covered by the studies.

These results represent a fundamental element of a comprehensive quantitative approach that could effectively support public health policies (Guariso et al. 2016). The DPSIR scheme adopted by the European Environment Agency (EEA 2012) represents a link between the scientific knowledge and methods and the need of decision makers design effective environmental plans. The DPSIR analytical concept is the causal framework for describing the interactions between society and environment. It includes the assessment of the State of the system, as the result of the Pressures exerted on the environment by human and natural activities or interventions (Drivers). The alteration of environmental conditions, inducing adverse Impacts on human health, vegetation, and ecosystem, requires actions (Responses) aimed at improving the environmental system quality. The actions are related to human activity and needs changes (Drivers), to emission reduction measures (Pressure), on direct concentration reductions (State), or on impact attenuation (Impacts). Turrini et al. (Turrini et al. 2017) is an example of the implementation of such decision framework on a regional domain including the study area of this paper.

In conclusion, more studies should be conducted in order to effectively identify criticisms that negatively affect the population health, even in synergy with an integrated assessment modeling, that combine environmental exposure and health risks and decision models. These could be helpful to the public policy-makers, to improve the protection of citizens and the environment.

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Abbreviations ACS, Acute coronary syndrome; AF, Atrial fibrillation; AHF, Acute hear failure; AST/ALT, Aspartate transaminase/alanine transaminase; Asth, Asthma; BG, Bergamo city; BS, Brescia city; BOLD, Blood-oxygen-level dependent; CFB, Cognitive function and behavior; CMM, Cutaneous malignant melanoma; CVD, Cardiovascular disease; df, Degree of freedom; DVT, Deep vein thrombosis; fMRI, Functional magnetic resonance imaging; IPD, Idiopathic Parkinson disease; IQ, Intelligent quotient; MN, Micronuclei; MVA, Malignant ventricular arrhythmia; NBF, Neurobehavioral function; NHL, Non-Hodgkin's lymphoma; OF, Olfactory function; OR, Odds ratio; PCBs, Polychlorinated biphenyls; PD, Parkinsonian disorders; RD, Respiratory disease; RR, Relative risk; SD, Standard deviation; SMR, standardized morbidity ratio; Thy, Thyroid hormones; UPDRS, Unified Parkinson's disease rating scale

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